

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property
Organization
International Bureau



(43) International Publication Date
10 March 2005 (10.03.2005)

PCT

(10) International Publication Number
WO 2005/020979 A1

(51) International Patent Classification: **A61K 31/198**,
9/48, A61P 5/48

(74) Common Representative: **RANBAXY LABORATO-**
RIES LIMITED; c/o DESHMUKH, Jay, R., 600 College
Road East, Suite 2100, Princeton, NJ 08540 (US).

(21) International Application Number:
PCT/IB2004/051678

(81) Designated States (unless otherwise indicated, for every
kind of national protection available): AF, AG, AI, AM,
AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN,
CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI,
GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE,
KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD,
MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG,
PI, PL, PT, RO, RU, SC, SD, SE, SG, SK, SI, SY, TJ, TM,
TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM,
ZW.

(22) International Filing Date:
2 September 2004 (02.09.2004)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
1100/DEL/2003 3 September 2003 (03.09.2003) IN

(84) Designated States (unless otherwise indicated, for every
kind of regional protection available): ARIPO (BW, GI,
GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM,
ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM),
European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI,
FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI,
SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ,
GW, ML, MR, NE, SN, TD, TG).

(71) Applicant (for all designated States except US): **RAN-**
BAXY LABORATORIES LIMITED [IN/IN]; 19, Nehru
Place, New Delhi, Delhi 110019 (IN).

(72) Inventors; and

(75) Inventors/Applicants (for US only): **SINGH, Roni**,
Barat [IN/IN]; A-14, Badshah Bagh, Varanasi, Uttar
Pradesh 221002 (IN). **SHILPA, Anu** [IN/IN]; Street
1-6, IIT Campus, New Delhi, Delhi 110016 (IN). **NA-**
GAPRASAD, Vishnubhotla [IN/IN]; 102 Surya Niwas
Apartments Balaji Nagar, Kukatpally, Hyderabad, Andhra
Pradesh 500072 (IN). **SETHI, Sanjeev, Kumar** [IN/IN];
House No. 365, Sector - 8, Faridabad, Haryana 121006
(IN).

Published:

- with international search report
- before the expiration of the time limit for amending the
claims and to be republished in the event of receipt of
amendments

For two-letter codes and other abbreviations, refer to the "Guid-
ance Notes on Codes and Abbreviations" appearing at the begin-
ning of each regular issue of the PCT Gazette.

WO 2005/020979 A1

(54) Title: A PROCESS FOR THE PREPARATION OF PHARMACEUTICAL COMPOSITIONS OF NATEGLINIDE

(57) Abstract: The present invention relates to a pharmaceutical composition comprising nateglinide, and a process for its prepara-
tion.

Description

A PROCESS FOR THE PREPARATION OF PHARMACEUTICAL COMPOSITIONS OF NATEGLINIDE

Technical Field

- [1] The present invention relates to a pharmaceutical composition comprising nateglinide, and a process for its preparation.

Background Art

- [2] Nateglinide is an amino acid derivative that lowers blood glucose levels by stimulating insulin secretion from the pancreas. It is widely indicated as monotherapy to lower blood glucose in patients with Type 2 diabetes. It is also indicated for use in combination with other anti-diabetic compounds, such as Metformin.
- [3] Nateglinide is insoluble in water. This physical property creates unpredictable dissolution rates and leads to absorption problems.
- [4] U.S. Patent No. 5,463,116 describes a method for producing a crystalline form of nateglinide having improved stability over the B-type crystals. B-type crystals suffer from problems of instability especially when subjected to mechanical grinding or pulverization. This instability results in the conversion of B-type crystals into other forms.
- [5] U.S. Patent No. 6,559,188 describes compositions of nateglinide or a pharmaceutically acceptable salt thereof wherein lactose and microcrystalline cellulose are used as fillers alone or in combination. The final formulation is formed without a pulverization step.
- [6] The most common approach used to address the problem of poor solubility is by reducing the drug's particle size or micronizing the drug to a size of few a microns. These strategies increase the effective surface area of nateglinide and thus improving the solubility. Dosage forms containing micronized drug particles exhibit enhanced solubility and consequently an improved bioavailability. Highly micronized drug particles possess poor flow properties and increased chances of re-agglomeration during processing. In few cases, re-agglomeration of micronized drug particles may be so problematic that the essential concept of enhancing the solubility by increasing the effective surface area is defeated.
- [7] In the present invention we have found that when nateglinide is co-sifted and/or co-milled with pharmaceutical inert carriers, these inert carriers give a 'cushioning effect' to nateglinide, which leads to stable dosage forms with an enhanced dissolution profile. Finely milled particles possess a high surface energy and charge on them. A pharmaceutical inert carrier helps in neutralizing the surface charge by providing a layer between two particles and thereby separating them. This separation of particles leads to an increase in surface area and improved dissolution.

Disclosure

- [8] Summary of the Invention

- [9] In one general aspect there is provided a process for the preparation of an oral pharmaceutical composition of nateglinide. The process includes co-milling nateglinide and one or more pharmaceutically inert carriers to form a blend; granulating the blend to form granules; drying and sizing the granules; and compressing the granules into tablets or filling into capsules. The nateglinide may be the Form B or the Form H type crystal modification.
- [10] Embodiments of the process may include one or more of the following features. For example, the pharmaceutically inert carrier may be one or more of silicate derivatives, cellulose derivatives and clays.
- [11] The silicate derivatives may be one or more of colloidal silicon dioxide, magnesium silicate, magnesium trisilicate, magnesium and aluminum silicate. For example, the silicate derivative may be colloidal silicon dioxide.
- [12] The cellulose derivatives may be one or more of microcrystalline cellulose and carboxymethylcellulose.
- [13] The clays may be one or more of veegum, bentonite and mixtures thereof.
- [14] The ratio of nateglinide to the pharmaceutically inert carrier may be in a range from about 10:1 to about 1:2. The nateglinide may have a particle size of $d_{90} < 45 \mu\text{m}$ or may have a particle size of $d_{90} < 30 \mu\text{m}$.
- [15] Embodiments of the process may also include one or more pharmaceutically acceptable excipients with the co-milled blend prior to granulation. The one or more pharmaceutically acceptable excipients may include fillers, binders, disintegrants, surfactants, lubricants, colorings and flavoring agents.
- [16] The process may also include at least one other anti-diabetic compound with the co-milled blend prior to granulation. The antidiabetic compound may be glitazones, sulfonyl urea derivatives and metformin, either in free form or in form of a pharmaceutically acceptable salt.
- [17] Tablets produced by the process may be coated with one or more functional and/or non-functional layers.
- [18] The co-milling carried out in the process may be done with an air jet mill, a multi mill, or a ball mill.
- [19] In another general aspect there is provided a process for the preparation of an oral pharmaceutical composition of nateglinide. The process includes co-sifting nateglinide and one or more pharmaceutically inert carriers to form a blend; granulating the blend to form granules; drying and sizing the granules; and compressing the granules into tablets or filling into capsules. The nateglinide may be the Form B or the Form H type crystal modification.
- [20] Embodiments of the process may include one or more of the following features. For example, the pharmaceutically inert carrier may be one or more of silicate derivatives, cellulose derivatives and clays.
- [21] The silicate derivatives may be one or more of colloidal silicon dioxide, magnesium

silicate, magnesium trisilicate, magnesium and aluminum silicate. For example, the silicate derivative may be colloidal silicon dioxide.

- [22] The cellulose derivatives may be one or more of microcrystalline cellulose and carboxymethylcellulose.
- [23] The clays may be one or more of veegum, bentonite and mixtures thereof.
- [24] The ratio of nateglinide to the pharmaceutically inert carrier may be in a range from about 10:1 to about 1:2. The nateglinide may have a particle size of $d_{90} < 45 \mu\text{m}$ or may have a particle size of $d_{90} < 30 \mu\text{m}$.
- [25] Embodiments of the process may also include one or more pharmaceutically acceptable excipients with the co-sifted blend prior to granulation. The one or more pharmaceutically acceptable excipients may include fillers, binders, disintegrants, surfactants, lubricants, colorings and flavoring agents
- [26] The process may also include at least one other anti-diabetic compound with the co-milled blend prior to granulation. The antidiabetic compound may be glitazones, sulfonyl urea derivatives and metformin, either in free form or in form of a pharmaceutically acceptable salt.
- [27] Tablets produced by the process may be coated with one or more functional and/or non-functional layers.
- [28] In yet another general aspect there is provided an oral pharmaceutical composition that includes nateglinide or pharmaceutically acceptable salts thereof and one or more pharmaceutically inert carriers. The nateglinide or a pharmaceutically acceptable salt thereof may have a particle size of $d_{90} < 30 \mu\text{m}$.
- [29] In a final general aspect there is provided a method for the treatment of metabolic disorders, type 2 diabetes mellitus, or a disease or condition associated with diabetes mellitus. The method includes administering to a patient in need thereof a pharmaceutical composition that includes nateglinide or pharmaceutically acceptable salts thereof; and one or more pharmaceutically inert carriers. The nateglinide or a pharmaceutically acceptable salt thereof may have a particle size of $d_{90} < 30 \mu\text{m}$.
- [30] Detailed Description of the Invention
- [31] The term 'nateglinide' as used herein includes nateglinide base as well as pharmaceutically acceptable salts thereof, in crystalline or amorphous form. For example, the nateglinide may be the B- or H-type crystal modification. The particle size of the nateglinide may be $d_{90} < 45 \mu\text{m}$, or may be $d_{90} < 30 \mu\text{m}$.
- [32] The term 'pharmaceutically inert carrier' refers to a substance, which is physiologically acceptable and compatible with the drug and other excipients in the dosage form and has a large surface area for drug particle adsorption. By virtue of such adsorption, the effective surface area exposed to the dissolution media is increased many fold, which thereby increases the rate of dissolution. Such adsorption of the drug on the inert carrier's surface also prevents the re-agglomeration of drug particles due to the neutralization of surface charges on the drug particles generated during milling.

Carriers also help in the wetting of a drug. These inert carriers improve the uptake of water by capillary action, thereby enhancing the drug's dissolution rate. Further, the inert carriers also form a layer around the drug which provides a 'cushioning effect'. Due to this layer around the drug, the drug remains stable even upon the application of external stress. The ratio of nateglinide to the pharmaceutically inert carriers may be in the range of about 10:1 to about 1:2.

- [33] Suitable pharmaceutically inert carriers include one or more of silicate derivatives such as, magnesium silicate, colloidal silicon dioxide, magnesium trisilicate, magnesium aluminum silicate; cellulose derivatives such as, microcrystalline cellulose, carboxymethylcellulose; and clays such as, veegum, bentonite and mixtures thereof. For example, colloidal silicon dioxide may be used alone or in combination with other cellulose derivatives.
- [34] The process of co-milling nateglinide and pharmaceutically inert carriers may be carried out in one or more conventional milling instruments including air jet mill, multi mill, ball mill or any other method of particle attrition. For example, the process of co-milling nateglinide with colloidal silicon dioxide may be carried out in an accelerated air-jet mill.
- [35] The process of co-sifting nateglinide with colloidal silicon dioxide may be carried out by mixing and co-sifting repeatedly till a uniform mixture is formed.
- [36] The co-sifted and/or co-milled mixture of nateglinide and pharmaceutically inert carriers may be further processed with pharmaceutically acceptable excipients into various dosage forms including one or more of tablets, capsules, and pills. These dosage forms, may be made by one or more of comminuting, mixing, granulation, melting, sizing, filling, drying, molding, immersing, coating, and compressing.
- [37] Pharmaceutical compositions of nateglinide may be prepared by the process of blending co-sifted and/or co-milled mixtures with one or more pharmaceutically acceptable excipients; wet granulating the blend with a granulating fluid or solution/dispersion of pharmaceutically acceptable excipients in the granulating fluid; drying and sizing the granules; and compressing the granules into tablets or filling into capsules.
- [38] Pharmaceutical compositions of nateglinide may also be prepared by the process of blending the co-sifted and/or co-milled mixture with one or more pharmaceutically acceptable excipients; dry granulating the blend with a roller compactor or slugging; drying and sizing the granules; and compressing the granules into tablets or filling into capsules.
- [39] Pharmaceutical compositions of nateglinide Form B, which have a particle size of $d_{90} < 45 \mu\text{m}$, may be prepared by the process of blending the co-sifted and/or co-milled mixture with one or more pharmaceutically acceptable excipients; and compressing the blend into tablets or filling into capsules.
- [40] The co-sifted/co-milled mixture of nateglinide and inert carriers may be further

mixed with one or more anti-diabetic compound prior to granulation. Suitable compounds include one or more of glitazones, sulfonyl urea derivatives and metformin. These compounds may be in free form or in the form of a pharmaceutically acceptable salt.

- [41] The term 'pharmaceutically acceptable excipient' refers to ingredients of the composition, excluding the active drug substance.
- [42] Suitable pharmaceutically acceptable excipients include one or more of fillers, binders, disintegrants, lubricants, glidants, and colors.
- [43] Suitable fillers include one or more of corn starch, lactose, white sugar, sucrose, sugar compressible, sugar confectioners, glucose, sorbitol, calcium carbonate, calcium phosphate-dibasic, calcium phosphate-tribasic, calcium sulfate, microcrystalline cellulose, silicified microcrystalline cellulose, cellulose powdered, dextrates, dextrans, dextrose, fructose, kaolin, lactitol, mannitol, sorbitol, starch, starch pregelatinized, and sucrose.
- [44] Suitable binders include one or more of methyl cellulose, hydroxypropyl cellulose, polyvinylpyrrolidone, gelatin, gum Arabic, ethyl cellulose, polyvinyl alcohol, pullutan, pregelatinized starch, agar, tragacanth, sodium alginate, and propylene glycol.
- [45] Suitable disintegrants include one or more of starch, croscarmellose sodium, crospovidone, and sodium starch glycolate.
- [46] Suitable lubricants and glidants include one or more of colloidal anhydrous silica, stearic acid, magnesium stearate, calcium stearate, talc, hydrogenated castor oil, sucrose esters of fatty acids, microcrystalline wax, yellow beeswax, and white beeswax.
- [47] Suitable coloring agents include one or more FDA approved colors for oral use.
- [48] The tablets prepared by the present invention may be coated with one or more additional layers of film forming agents and/or pharmaceutically acceptable excipients.
- [49] The coating layers over the tablet may be applied as a solution/ dispersion of coating ingredients using any conventional technique known in the prior art including spray coating in a conventional coating pan, fluidized bed processor; and dip coating.
- [50] Suitable solvents used for preparing a solution/dispersion of the coating ingredients include one or more of methylene chloride, isopropyl alcohol, acetone, methanol, ethanol, water and mixtures thereof.
- [51] Suitable film forming agents include one or more of ethyl cellulose, hydroxypropyl methylcellulose, hydroxypropyl cellulose, methyl cellulose, carboxymethylcellulose, hydroxymethylcellulose, hydroxyethylcellulose, hydroxypropyl methyl phthalate, cellulose acetate, cellulose acetate trimellitate, cellulose acetate phthalate; Waxes, such as, polyethylene glycol; methacrylic acid polymers, such as, Eudragit® RL and RS; and mixture thereof. Commercially available coating compositions marketed under various trade names, such as Opadry® may also be used for coating.
- [52] The following examples are illustrative of the invention, and are not to be

construed as limiting the invention.

[53] **TABLE 1**

Ingredients	Example 1 (wt/tablet) mg	Example 2 (wt/tablet) mg
Nateglinide	120*	120**
Lactose monohydrate	325	325
Colloidal silicon dioxide	28	28
Microcrystalline cellulose	86	86
Polyvinyl Pyrrolidone	12	12
Croscarmellose sodium	20	20
Sodium Lauryl Sulphate	12	12
Purified water	q.s	q.s
Croscarmellose Sodium	12.8	12.8
Colloidal silicon dioxide	12.8	12.8
Magnesium stearate	11.4	11.4

[54] * Particle size d90 = 46 μ m

[55] ** Particle size d90 = 22 μ m

[56]

PROCEDURE:

1. Colloidal silicon dioxide and nateglinide are co-sifted by mixing repeatedly till a uniform mixture is formed.
2. The co-sifted mixture of step 1 along with microcrystalline cellulose, lactose monohydrate and a part of croscarmellose sodium are mixed in a high shear mixer and granulated using aqueous solutions that include sodium lauryl sulphate and polyvinyl pyrrolidone.
3. The wet granules are dried in a fluid bed drier, passed through a screen and then milled.
4. The colloidal silicon dioxide and the rest of the croscarmellose sodium are mixed, passed through a screen and blended with the mixture of step 3.
5. The magnesium stearate is passed through a screen, blended with the blend of step 4 and the resulting mixture is compressed to tablets.

[57]

[58] **TABLE II**

Ingredients	Example 3 (wt/tablet) mg	Example 4 (wt/tablet) mg
Nateglinide	120*	120**

Lactose monohydrate	325	325
Colloidal silicon dioxide	14	14
Microcrystalline cellulose	74	74
Polyvinyl Pyrrolidone	12	12
Sodium Starch Glycolate	67.3	67.3
Sodium Lauryl Sulphate	24	24
Purified water	q.s	q.s
Sodium Starch Glycolate	39.7	39.7
Colloidal silicon dioxide	12.8	12.8
Magnesium stearate	11.2	11.2

[59] * Particle size $d_{90} = 27 \mu\text{m}$

[60] ** Particle size $d_{90} = 8 \mu\text{m}$

[61]

PROCEDURE:

[62]

1. Colloidal silicon dioxide and nateglinide are co-sifted repeatedly and mixed together in a low shear blender.
2. The co-sifted mixture of step 1 along with microcrystalline cellulose, lactose monohydrate and a part of sodium starch glycolate are mixed in a high shear mixer and granulated using aqueous solutions containing sodium lauryl sulphate and polyvinyl pyrrolidone.
3. The wet granules are dried in a fluid bed drier, passed through a screen and milled.
4. The colloidal silicon dioxide and the rest of the sodium starch glycolate are mixed, passed through a screen and blended with the mixture of step 3.
5. The magnesium stearate is passed through a screen, blended with the blend of step 4 and the total mixture is compressed into tablets.

[63]

Comparative *In vitro* dissolution study

[64] The *In vitro* release profile of nateglinide from tablets as per Examples 1-4 were studied in 1000 ml, 0.01 N HCl, with 0.5% SLS (pH-1.2), using USP apparatus - II, at 50 rpm. The results are listed in Table 3.

[65]

TABLE 3

Time (min)	Percentage (%) of Nateglinide released				

	Example1	Example 2	Example 3	Example 4	Starlix
10	51	97	72	85	74
20	73	97	89	98	86
30	79	98	97	102	94

[66] Table 3 indicates that compositions having nateglinide particle size $d_{90} < 45 \mu\text{m}$ show a better dissolution profile as compared to the compositions having particle size $d_{90} > 45 \mu\text{m}$.

[67] While the present invention has been described in terms of its specific embodiments, certain modifications and equivalents will be apparent to those skilled in the art and are included within the scope of the present invention.

Claims

- [1] A process for the preparation of an oral pharmaceutical composition of nateglinide, the process comprising:
- a. co-milling nateglinide and one or more pharmaceutically inert carriers to form a blend;
 - b. granulating the blend to form granules;
 - c. drying and sizing the granules; and
 - d. compressing the granules into tablets or filling into capsules.
- [2] The process according to claim 1, wherein the nateglinide comprises Form B or Form H type crystal modification.
- [3] The process according to claim 1, wherein the nateglinide comprises Form B type crystal modification.
- [4] The process according to claim 1, wherein the pharmaceutically inert carrier comprises one or more of silicate derivatives, cellulose derivatives and clays.
- [5] The process according to claim 4, wherein the silicate derivatives comprise one or more of colloidal silicon dioxide, magnesium silicate, magnesium trisilicate, magnesium and aluminum silicate.
- [6] The process according to claim 4, wherein the cellulose derivatives comprise one or more of microcrystalline cellulose and carboxymethylcellulose.
- [7] The process according to claim 4, wherein the clays comprise one or more of veegum, bentonite and mixtures thereof.
- [8] The process according to claim 1, wherein the pharmaceutically inert carrier comprises colloidal silicon dioxide.
- [9] The process according to claim 1, wherein the ratio of nateglinide to the pharmaceutically inert carrier comprises a range from about 10:1 to about 1:2.
- [10] The process according to claim 1, wherein the nateglinide has a particle size of $d_{90} < 45 \mu\text{m}$.
- [11] The process according to claim 1, wherein the nateglinide has a particle size of $d_{90} < 30 \mu\text{m}$.
- [12] The process according to claim 1, further comprising mixing one or more pharmaceutically acceptable excipients with the co-milled blend prior to granulation.
- [13] The process according to claim 1, further comprising mixing at least one other anti-diabetic compound with the co-milled blend prior to granulation.
- [14] The process according to claim 13, wherein the antidiabetic compound comprises glitazones, sulfonyl urea derivatives and metformin, either in free form or in form of a pharmaceutically acceptable salt.
- [15] The process according to claim 12, wherein the one or more pharmaceutically acceptable excipients comprise fillers, binders, disintegrants, surfactants, lubricants, colorings and flavoring agents.
- [16] The process according to claim 1, wherein the tablet is further coated with one or

- more functional and/or non-functional layers.
- [17] The process according to claim 1, wherein the co-milling is done with an air jet mill, a multi mill, or a ball mill.
- [18] A process for the preparation of an oral pharmaceutical composition of nateglinide, the process comprising:
- a. co-sifting nateglinide and one or more pharmaceutically inert carriers to form a blend;
 - b. granulating the blend to form granules;
 - c. drying and sizing the granules; and
 - d. compressing the granules into tablets or filling into capsules.
- [19] The process according to claim 18, wherein the nateglinide comprises Form B or Form H type crystal modification.
- [20] The process according to claim 18, wherein the nateglinide comprises Form B type crystal modification.
- [21] The process according to claim 18, wherein the pharmaceutically inert carrier comprises one or more of silicate derivatives, cellulose derivatives and clays.
- [22] The process according to claim 21, wherein the silicate derivatives comprise one or more of colloidal silicon dioxide, magnesium silicate, magnesium trisilicate, magnesium and aluminum silicate.
- [23] The process according to claim 21, wherein the cellulose derivatives comprise one or more of microcrystalline cellulose and carboxymethylcellulose.
- [24] The process according to claim 21, wherein the clays comprise one or more of veegum, bentonite and mixtures thereof.
- [25] The process according to claim 18, wherein the pharmaceutically inert carrier comprises colloidal silicon dioxide.
- [26] The process according to claim 18, wherein the ratio of nateglinide to the pharmaceutical inert carrier comprises a range from about 10:1 to about 1:2.
- [27] The process according to claim 18, wherein the nateglinide has a particle size of $d_{90} < 45 \mu\text{m}$.
- [28] The process according to claim 18, wherein the nateglinide has a particle size of $d_{90} < 30 \mu\text{m}$.
- [29] The process according to claim 18, further comprising mixing one or more pharmaceutically acceptable excipients with the co-sifted blend prior to granulation.
- [30] The process according to claim 18, further comprising mixing at least one other anti-diabetic compound with the co-milled blend prior to granulation..
- [31] The process according to claim 30, wherein the antidiabetic compound comprises glitazones, sulfonyl urea derivatives and metformin, either in free form or in form of a pharmaceutically acceptable salt.
- [32] The process according to claim 29, wherein the one or more pharmaceutically acceptable excipients comprise fillers, binders, disintegrants, surfactants,

lubricants, colorings and flavoring agents.

[33] The process according to claim 18, wherein the tablet is further coated with one or more functional and/or non-functional layers.

[34] An oral pharmaceutical composition comprising:

a. ateglinide or pharmaceutically acceptable salts thereof; and

b. one or more pharmaceutically inert carriers,

wherein the nateglinide or a pharmaceutically acceptable salt thereof has a particle size of $d_{90} < 30 \mu\text{m}$.

[35] A method for the treatment of metabolic disorders, type 2 diabetes mellitus, or a disease or condition associated with diabetes mellitus, the method comprising administering to a patient in need thereof a pharmaceutical composition comprising:

a. ateglinide or pharmaceutically acceptable salts thereof; and

b. one or more pharmaceutically inert carriers,

wherein the nateglinide or a pharmaceutically acceptable salt thereof has a particle size of $d_{90} < 30 \mu\text{m}$.

INTERNATIONAL SEARCH REPORT

 Int. Application No
 PCT/IB2004/051678

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61K31/198 A61K9/48 A61P5/48

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

 Minimum documentation searched (classification system followed by classification symbols)
 IPC 7 A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No
P,X	US 2004/002544 A1 (MAKINO CHISATO ET AL) 1 January 2004 (2004-01-01) paragraphs '0052!', '0053!', '0078!; claims 1-35	1,18,34, 35
X	EP 1 258 249 A (AJINOMOTO CO., INC) 20 November 2002 (2002-11-20) paragraphs '0042!', '0045!', '0051!', '0052!; claims 1-23; examples 1,20,21	1,18,34, 35
X	US 6 559 188 B1 (GATLIN MARJORIE REGAN ET AL) 6 May 2003 (2003-05-06) cited in the application column 16, line 26 - line 38; claims 1-6,9,10	1,18,34, 35
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☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex

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Date of the actual completion of the international search

27 January 2005

Date of mailing of the international search report

15/02/2005

Name and mailing address of the ISA

 European Patent Office, P B 5818 Patentlaan 2
 NL - 2280 HV Rijswijk
 Tel. (+31-70) 340-2040, Tx 31 651 epo nl.
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INTERNATIONAL SEARCH REPORT

International Application No.
PCT/JP2004/051678

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO 03/076393 A1 (NOVARTIS AG; NOVARTIS PHARMA GMBH; SUTTON, PAUL, ALLEN; VIVILECCHIA, R) 18 September 2003 (2003-09-18) claims 1-24; example 9	1,18,34, 35
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INTERNATIONAL SEARCH REPORT

International application No.
PCT/182004/051678

Box II Observations where certain claims were found unsearchable (Continuation of Item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: —
because they relate to subject matter not required to be searched by this Authority, namely:
Although claim 35 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of Item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Int. Application No.
PCT/JP2004/051678

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